

■ **HUMANICS** is the scientific study of human nature. It tells something of our past traditions that the word is an unfamiliar one; but the subject it describes is inevitably caught up in the recent rush of progress in experimental biology. In particular, dramatic advances in our knowledge of the biochemistry of deoxyribonucleic acid (DNA) and of its function as the material basis of heredity have provoked much new speculation about the application of this new knowledge to man and his problems. As a result of these advances, we anticipate better tools to mitigate disease, to improve agriculture, and to exploit microorganisms in industry.

We must also visualize, however, the impact of genetic engineering on humanics, which includes the possible modification of human nature toward previously unattainable ideals. Phrases like "genetic programming" or "genetic engineering" may conjure up the Frankensteinian image of a mad scientist or a technocratic dictator pushing the buttons that will control an assembly line of babies produced to order for service as infantrymen or storm troopers or docile subjects. Some may even imagine that their own genes may somehow be subjected to alteration at someone else's command or that they will have unlimited options to create any manner of offspring they wish—perhaps a child who might grow up as an athletic prodigy with an IQ of 350 and a head of hair that automatically shears itself at regular intervals.

Actually, our present knowledge of genetic science is not the obvious limiting factor for the furtherance of such aims. Rather, we lack the necessary insight into the essential biochemistry, developmental biology, psychology, and social dynamics of these phenomena. And indeed, were we to gain such insight, genetic engineering would probably be a redundant tool in competition with many other ways of influencing human development and behavior. To avoid the distorted view of genetic engineering that is all too prevalent in contemporary journalism, the topic must be examined within a broader view of man's evolutionary history and of the impact of established institutions on human biology.

Genetic engineering has been an important element in human cultural progress. The beginnings of agriculture depended on the remarkable insight that the seeds of a given plant would beget others like it. Early agricultural man, in his development of crops like

Indian corn and wheat, accomplished technical miracles that have still to be surpassed by contemporary plant science. This kind of "biological engineering"—to produce reliable food crops from wild grasses—achieved a phenomenal result without the benefit of profound insight into the mechanism of heredity or the chemistry of DNA.

We have no way of knowing whether prehistoric man consciously applied similar principles to guiding his own evolution by selective breeding. In many subhuman primates the social hierarchy does give a dominant male privileged access to receptive females during their intervals of maximum fertility. With the development of democratic ideals, however, the very concept of compulsory selective breeding as a method of engineering human improvement has been discredited as a violation of elementary human rights.

The principal utility of genetics in modern medicine is in diagnosis, now applicable to many specific genetic diseases with great precision, mainly by the use of biochemical and microscopic methods. It is often possible to counsel parents in a family where a rare disease has cropped up about the prospects of a similar anomaly occurring again in future children. Since many parents will respond to discouraging advice by not taking chances, this kind of genetic counseling is a *de facto* form of selective breeding. Its principal benefit, however, is intended to promote the integrity of the family and to prevent the conception of children likely to suffer from a serious defect. A by-product of genetic counseling in this situation is to reduce the frequency of defective genes in the next generation.

Because certain deleterious genes also can be detected in the hybrid carrier state, some individuals may use this information in their selection of mates. As yet, we have no reliable statistical information on the subject, but it is doubtful that any significant number of people take genetic factors into account when they fall in love and marry.

From a population-genetic point of view, selective mating does not help to eliminate a deleterious gene from the population; it merely postpones the overt occurrence of defective offspring. Since future generations may well be better equipped to repair a genetic defect than we are at the present time, selective mating can hardly be called an imprudent policy. (*Turn page*)

Doctor Lederberg, chairman of the Department of Genetics, Stanford University, won the 1958 Nobel prize in medicine for studies on the organization of genetic material in bacteria. His writings include significant observations on genetics, chemistry, and the evolution of man. But there is controversy among scientists over the outlook for genetic engineering in humans. For another view, see "George Beadle Talks About the New Genetics," TODAY'S HEALTH, July 1969.

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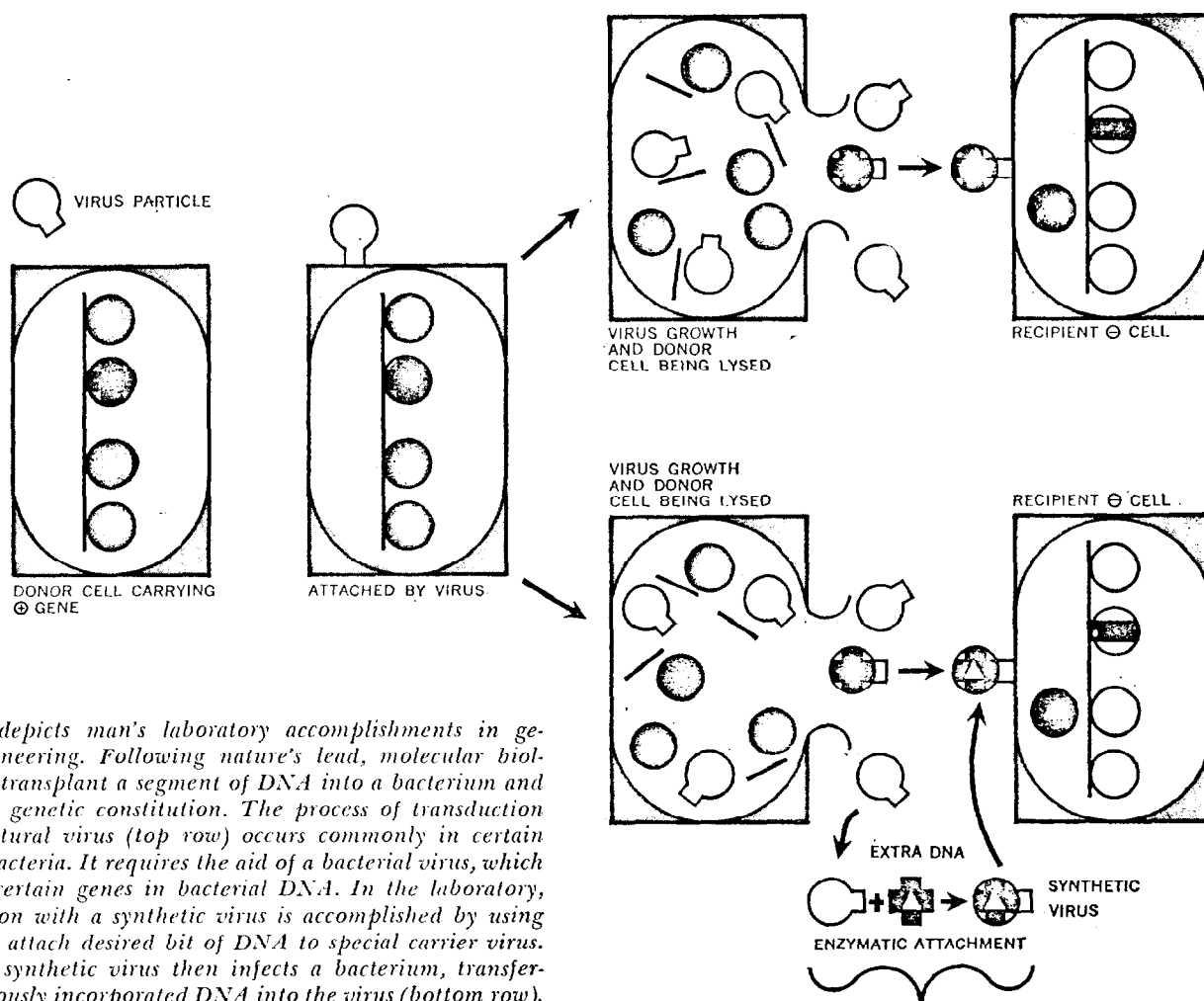


Diagram depicts man's laboratory accomplishments in genetic engineering. Following nature's lead, molecular biologists can transplant a segment of DNA into a bacterium and change its genetic constitution. The process of transduction with a natural virus (top row) occurs commonly in certain kinds of bacteria. It requires the aid of a bacterial virus, which displaces certain genes in bacterial DNA. In the laboratory, transduction with a synthetic virus is accomplished by using enzyme to attach desired bit of DNA to special carrier virus. Resulting synthetic virus then infects a bacterium, transferring previously incorporated DNA into the virus (bottom row).

The genetic diseases to which such considerations apply are each quite rare, but there are enough of them to warrant the spreading practice of genetic diagnosis in order to furnish significant information to a considerable proportion of the population. The average human being carries the equivalent of eight or 10 potentially harmful genetic defects, all of which are usually masked in the hybrid condition. Although most of these defects are not now recognizable by biochemical analysis, studies of DNA specificity and of cell fusion are beginning to revolutionize our approach to these problems.

Cell cultures from specimens of blood or from tiny fragments of skin have enhanced the diagnosis of many genetic diseases. More recently, this technique has also been applied to cells obtained from the amniotic fluid that surrounds the developing fetus. By this method the occurrence of a serious genetic disease in a young fetus can be diagnosed, and the mother may request a therapeutic abortion to avoid bearing a severely crippled or retarded child. [In many states, this request cannot be granted legally.]

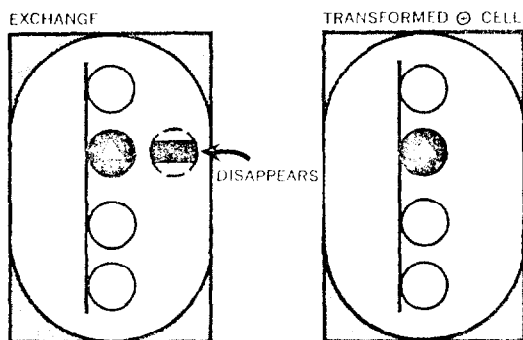
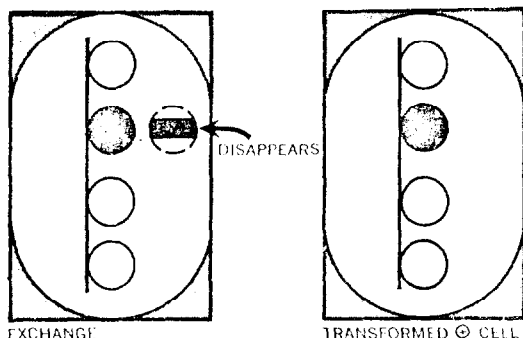
A number of genetic diseases can now be detected prenatally. Of these cystic fibrosis, a metabolic disorder in children, is the most prevalent. Its incidence, however, is too rare to recommend the routine examination

of amniotic fluid in every pregnancy. On the other hand, the carrier state for cystic fibrosis can also be determined in the parents, and fetal examination would be indicated if there is already one chance in four that the fetus may be diseased.

While the elimination of fetuses having this serious genetic disease may appear to be a negative approach, this procedure should be weighed against the assurance that can be given parents of being able to nurture a child free from disease on future attempts. Eventually, a better understanding of the biochemistry of cystic fibrosis may lead to methods of treatment so effective that the disease would no longer be a serious burden to the young child.

In many respects, mongolism, or Down's syndrome, is more serious than cystic fibrosis because of its severe mental retardation. Prenatal examination can reveal the extra chromosome that causes the condition. Down's syndrome occurs in one of about 600 births, but certain individuals have a chromosome pattern that predisposes them to a much higher frequency of afflicted progeny. For such mothers, and mothers with pregnancies at advanced ages, a prenatal examination of fetal cells is especially indicated.

Paradoxically, additional conceptions undertaken to compensate for an eliminated fetus will tend to increase



Progress in Cellular Engineering

While genetic engineering someday may have revolutionary effects on medicine—and on mankind—another type of “biological engineering” is already saving lives.

Called cellular engineering, it is a technique in which the bone marrow of one person is transplanted into another. Today it is being used to treat patients with certain hereditary defects, such as Wiskott-Aldrich syndrome and lymphopenic agammaglobulinemia. Infants with one of these rare immunologic deficiency diseases (the inability to resist infections) have been injected with marrow cells “borrowed” from members of their families. When the transplanted bone marrow (the organ which manufactures disease-fighting corpuscles) “takes,” it provides their bodies with the ability to protect themselves.

In cellular engineering, whole cells are transplanted. In genetic programming, on the other hand, scientists must deal with the DNA molecule within the chromosome within the nucleus of the cell. Partly because of this, many experts feel that cellular engineering may produce more immediate results in humans than genetic engineering.

But its future is by no means assured. Even with recently developed tissue-typing methods, there have been marrow transplant failures because of rejection. Further research into cell compatibility is needed. So far, cells from immediate family members have been used in most successful transplants. Research continues using donors outside the family.

In addition, no one knows what the long-term effects of cellular engineering will be. Only about a dozen of these operations have been successful. The longest living bone marrow transplant patients have survived slightly more than one year. But the early results seem encouraging.

“We are at the threshold of cellular engineering,” observes Dr. Robert A. Good, professor of pediatrics and microbiology, University of Minnesota. “If we can cross this threshold, we will be able to attack many other diseases.”

In addition to various birth defect diseases, future targets of cellular engineering include certain types of cancer—chiefly leukemia—with associated immunologic deficiencies, liver and kidney diseases, and some types of inborn errors of metabolism. Some limited successes in leukemia research already have been achieved.

“There are many problems that must be solved first,” Doctor Good acknowledges. “But the challenges of the future are exciting.”

the frequency of the deleterious gene in the population. For example, the child with cystic fibrosis was, until recently, not likely to survive until reproductive age and, therefore, did not contribute to the gene pool of the following generation. Also, the diseased child tended to displace a potential sibling whose odds are two in three of being a carrier for the gene and who would eventually contribute to the gene pool.

If, however, our objective in this kind of medicine is to alleviate unnecessary human distress, then we should focus our attention on the reduction of the disease, rather than on the elimination of the gene for it. In spite of the obvious natural selection against it, the gene's very capacity to survive in the human population indicates that it might also carry some still unexplained and even beneficial function in human fitness.

Another characteristic that can be diagnosed by prenatal examination is the sex of the fetus. Improved determination of fetal sex at an early age and the development of drugs to induce a voluntary abortion may make individual control of the sex of offspring technically plausible. The use of abortion for this purpose, however, would probably be repugnant to most people.

Germinal choice, which is another approach to selective breeding, has been advocated strongly by Julian Huxley and the late [geneticist] (Continued on page 80)

set of genes could forestall the possibility of a disease developing in a person, any disease can then be said to have a genetic aspect. Preventive measures, such as the Sabin vaccine for polio, can be regarded as artificial replacement of the human genes that are unequal to this one of life's challenges. We do not know, however, whether any living human beings already contain genetic factors for resistance to polio virus. If they did, the comparison of resistant and sensitive individuals would put the genetic aspect of this kind of medicine into sharper focus.

The brain, in its growth, must be subject to some explicit regulation from external stimuli. This is an urgent item on the humanist's agenda. We need powerful tools to deal, on the one hand, with obvious defects that cry out to be corrected and, on the other, with the possible enhancement of human intellectual ability. The closest parallel to this in present practice is the care that physicians take to be sure that pregnant mothers do not suffer from thyroid deficiency.

Another approach to the modification of an established genetic makeup is the transplantation of the tissue or organ from another individual. When the indication for such a transplant is a failing heart or kidney, obviously the operation is not a compensation for a genetic defect. The message is clearer, however, when the indication is a metabolically insufficient pancreas—say diabetes, though the primary lesion may be elsewhere—or a congenital deficiency in some other endocrine gland.

Tissue transplantation is still seriously impeded by two factors: the phenomenon of tissue rejection based on genetic incompatibility of different individuals and the serious difficulty of obtaining viable organs for transplant. Fundamental genetic studies on the determination of the protein structure of antibodies and of tissue antigens may be expected to eliminate the first obstacle. As for organ supply, a thorough understanding of tissue rejection may make it possible to use animal organs for transplant purposes. One approach that would allow the use of animal organs would be the early inoculation of infants with purified pooled antigens representing the tissue specificities of potential future organ donors.

Transplantation, in the sense of mixing cells of different origin into one organism, can be done experimentally at very early stages of embryological development. Already, as many as four different mouse eggs, representing eight different parents, have been fused to form a single embryo that matured into a

single adult mouse. This procedure has great theoretical interest because of its potential for incorporating complementary advantages from a variety of different parental strains.

Except for a calculated choice of parentage, intelligent design plays a limited role in controlling the genetic makeup of an individual. In microorganisms, however, it is now possible to introduce specific new genetic information in a much more controlled fashion. But such experiments still have considerable random components, and usually it is not possible to instruct one particular cell to adopt a specific new genotype. Instead, a large number of cells are exposed to DNA that has been contrived to have the desired characteristics. One out of the many cells may incorporate the foreign DNA and with it some new characteristic. The occasional cell that responds in the appropriate fashion can then be separated from the other cells.

The great force of recent work in molecular biology stems from the use of relatively simple experimental materials, such as viruses and bacteria. The direct manipulation of individual genes within the chromosomes in cells of higher organisms, however, presents formidable and possibly insuperable technical difficulties. Nevertheless, we can foresee the use of viruses to mediate the transmission of specific genetic information.

Contemporary work with animal viruses by a number of scientists now strongly suggests that these viruses may also be capable of introducing genetic information in the cells that they infect. For example, the SV-40 virus of monkeys, which as far as is known is harmless in man, leaves a number of copies of its DNA sequences in the chromosomes of cells infected in tissue culture. This suggests that viral DNA can be engineered and that synthetic viruses can be used for the modification of genetic defects.

For instance, it should soon be technically feasible to attach the genetic DNA that codes for the enzyme phenylalanine hydroxylase, which functions in the liver of normal men and animals, to the DNA of SV-40 virus. The inoculation of an infant with such a hybrid virus would be expected to alleviate the disease phenylketonuria (PKU).

Man has, in fact, been practicing a similar form of genetic engineering for quite some time. When Edward Jenner discovered the vaccination against smallpox, he introduced the use of a variant virus to compensate for a "genetic defect" shared by all mankind—namely, our inherent sluggishness in producing antibodies against the smallpox virus.

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Genetic Engineering

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icist] Hermann J. Muller. Their scheme would provide for the banking of sperm from preferred men in cold storage for later voluntary use in artificial insemination. Real problems arise, of course, in the identification of preferred males.

However bizarre these schemes for selective breeding may appear, the present world does exhibit a wide disparity in the number of offspring produced by different parents. In some sense, our other social policies establish the pattern for these discrepancies. Yet, we know too little of human genetics to sustain an informed criticism (or approval) of that pattern. It is much more difficult not to be alarmed at some examples of negative family planning in relation to parents' ability to provide each child with the parental care that should be his birthright. On the other hand, we have still to devise compulsory schemes that can discourage overbreeding where it demeans a child's rights without at the same time creating an unacceptable invasion of the personal freedoms of the parents.

It is not easy to set clear boundaries for the subject of genetic intervention. Since one could postulate that the right

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The projected design for the use of more carefully engineered viruses to generate specific enzymes shows an obvious parallel to this long-established medical procedure.

This approach to genetic engineering also has the advantage that, in all likelihood, the genetic information carried by such viruses is not incorporated in the sex cells for transmission to the next generation. This is a purely empirical observation. To be sure of keeping future options open, the limitation of virogenetic effect to somatic tissues must be carefully verified in every case.

At this writing, only one important technical difficulty remains—that of attaching specific segments of DNA from totally unrelated sources. However, enzymes discovered in 1968 for rejoining DNA molecules broken in just one strand are already being used as essential reagents in research.

The theoretical possibility of virogenic attachment to chromosomes and propagation to further generations cannot be completely determined without empirical study. If we do not keep a vigilant lookout on the effects of viruses—whether used for vaccination against disease, for genetic repair, or as infectious agents in our environment—we may be in for some unpleasant surprises.

Because the use of viruses for vaccination purposes has not been generally associated with the alarms of "genetic engineering," these agents do not receive the close attention they deserve in view of their biological potentialities. At the very least, viruses used for vaccination should be chemically purified and identified as having only the one desired species of DNA or RNA (ribonucleic acid). This standard has not yet been adopted by the pharmaceutical industry, nor has it been included in the regulations enforced by governments.

The extraordinary specificity of pairing by the two strands of a DNA molecule has opened the way for studying biological specificity, mainly by molecular hybridization. The specific reagent in these experiments is a solution of DNA single strands prepared from reference material. For some purposes, this DNA may be incorporated into a culture medium of solid agar or attached to the surface of filter membranes. When exactly complementary strands of DNA, or sometimes RNA, are added, conventional double-stranded DNA structures will be re-formed and can be detected by a variety of different methods. Some of these methods are so sensitive that it may be possible to discern even single nucleotide differences between a reference and an unknown in a sample.

These procedures will, undoubtedly, be instrumental for the isolation of specific-gene DNA, an objective which has already been achieved to a limited extent. Molecular hybridization also furnishes a method of distinguishing from each other the messenger-RNAs produced by different cells.

Other advances in cell biology have opened up some additional technical possibilities for the evasion of genetic scrambling that now invariably accompanies sexual reproduction. The propagation of new plants from cuttings is a familiar experience in horticulture. In lower animals such as earthworms, vegetative reproduction is a common occurrence; missing organs can regenerate spontaneously in small fragments cut from the previous individual. Deeper insights into the mechanisms of this embryological development could lead to similar phenomena, even in man. But these are remote prospects indeed.

Groups of individuals derived by vegetative propagation and having identical genetic constitutions are called "clones." The prospect of producing genetically homogeneous groups of individuals presents some interesting issues. In addition, it is a way of propagating a genotype already tested in one generation for further trial in a second. We already have a foretaste of the properties of a clone in the behavior of identical twins.

Clonal propagation would afford an otherwise unavailable opportunity for certain humanic experiments. Without such tests it is unlikely that we will ever be able to know the extent to which the performance of acknowledged geniuses or athletic stars are manifestations of unusual genetic endowment.

The technical limitation to human cloning is mainly the much smaller size of mammalian eggs when compared with the egg of a frog, but this is not an insuperable difficulty. There may be, however, other obstacles based on differences in the biology of the frog egg and that of the human that are not yet known.

Within the last few years, it has been discovered that tissue cells can be made to fuse with one another in the presence of certain virus-derived particles. These cells thus form "vegetative hybrids" that can originate from such widely distinct species as fish and human. The technique has already become quite important in the analysis of the genetic functions carried by different human chromosomes, which can be tested for their ability to make up for known defects in other animal cells.

Vegetative hybridization and the use of the hybrid cells to renucleate an egg open the door to another form of ge-

netic engineering—hybrid plants or animals containing some or many chromosomes from distant species.

When we approach functions as complex as human intelligence and sympathy, we must be quite humble about our capacity to unravel the components of heredity and environment. Certainly, there is no gene that can ensure the ideal development of a child's brain without reference to tender care and inspired teaching. The paths to intelligence can be deviated at many points. For example, the child born deaf was, for all practical purposes, an idiot until we learned the special techniques needed to teach him.

These considerations suggest that the main role of genetic science may be to sharpen perceptions of how to engineer the environment for the optimum development of existing genetic types. When we have reached some mastery of this challenge, we can more reasonably advocate the extension of genetic engineering beyond the repair of the most obvious and urgent forms of genetic defect.

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